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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
PATEL, SUDHAKER B	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 05/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/725,212	GUNAWARDANA, INDRANI W.	
	Examiner	Art Unit	
	Sudhaker B. Patel, D.Sc.Tech.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *4/26/04* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Priority

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification of in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number.

Parent Data

" This application **is a continuation of** 09695040,filed 10/24/200,
Which is a continuation in part of 09541795, filed 3/31/200,
Which is a continuation in part of 09474517, filed 12/29/1999, now abandoned,
Which Claims Priority from Provisional Application 60114097, filed 12/29/1998" is suggested.

It is noted that this application appears to claim subject matter disclosed in other related prior Application No. 09222491, filed 12/29/1998. A reference and relationship to the prior application must be inserted as the first sentence of the specification of this application or in an application data sheet (37 CFR 1.76), if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e) or 120. See 37 CFR 1.78(a). For benefit claims under 35 U.S.C. 120, the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of all nonprovisional applications. Also, the current status of all nonprovisional parent applications referenced should be included.

Observations made during preliminary search:

(1). Preliminary examination and comparison of the instant U.S. Application Sr. No. 10725212 filed 12/1/2003 with the provisional U. S. Application Sr. No. 60114097, filed 12/29/097 shows that applicants have added new claims 24,25 which are related to intermediates, and new claims 32, 33 related to method of use for Cerebral Vasospasm. Therefore, the above stated ***new claims will only qualify for the priority date which is the filing date of instant application i.e. priority as of 12/1/2003.***

(2). It is recognized that applicants are urging benefit of **Provisional Application** 60114097, filed 12/29/1998, under 35 U.S.C. 120 and under 35 U.S.C. 119. However, to obtain such benefit, **claims must comply with 35 U.S.C. 112, paragraph one**, namely description and enablement as was set forth in In re Scheiber 199 USPQ 782; In re Chu 36 USPQ2d 1089.

Currently only the instant filing date is accorded the claims since subject matter claimed herein is not entirely described in the earlier parent, US ' 097. Compare instant claims32,33 with the ref.' 097 method of use claims 16-19.

(2). Preliminary search also revealed presence of other related Applications No. PCT/US99/31162 and PCT/US/00/08895, the subject matter of which is similar to that is claimed herein. Applicants are urged to disclose exact relationship of instant application to above stated and also any other applications (U.S. or foreign, if existing), because the same will constitute the material necessary for examination during the prosecution this application.

STATUS OF CLAIMS

Claims 1-8,26, -31 are related to compounds, claim 19 is related to pharmaceutical composition, claims 24,25 are related to intermediates, and claims 20-23 are related to method of use. Applicants have added new claims 32,33 are related to method of use. Therefore, claims in this application are the claims 1-33.

Claims 1,19, 20-23, 32,33 are of generic nature. See rejections bellow.

Examiner has considered above stated facts, and it is found that this application is not ready for allowance at this stage for reasons stated bellow. Claims 1,19, 20-23, 32,33 are of generic nature. Examiner has conducted search for compound, composition and a method of claims 1,11,19, 20-21 within the time made available and at disposal for an examination of the application to the examiner. **Should applicants decide to amend either specification or claims extensively, restriction/election will be necessary.** See rejections bellow.

Accordingly, first action on merits follows.

Double Patenting

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

2. Claims1, 19,20-23, and claims dependent on these claims are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1,15,16-19 of U.S. Patent No. 6110922. Although the conflicting claims are not identical, they are not patentably distinct from each other because the compounds of ref. '922 generic claim 1 (see columns 43-45), composition claim 15, method of use claims 16-19 overlap with the instant application. Therefore, if the instant application were patented, it would extend the monopoly of the patent already granted.

3. Claims1, 19,20-23, and claims dependent on these claims are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 15,16-19, 29,30,32,35,37, and claims dependent on these claims of copending Application No. 10356794, filed 8/29/02. Although the conflicting claims are not identical, they are not patentably distinct from each other because the compounds of ref.'794 generic claim 1, composition clam 15, and method

of use claims 16-19 overlap with the claims of instant application. Therefore, if this application were granted patent, it would extend the monopoly of the above stated application(s).

4. Claims1, 19,20-23,24,25 and claims dependent on these claims are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1,19, 20-23,24,25,45-46,47,48-51, and claims dependent on these claims of copending Application No. 09541795, filed 3/31/2000. Although the conflicting claims are not identical, they are not patentably distinct from each other because the compounds of ref.'795 generic claim 1, composition clams 19,47, intermediates' claims 24,25, and method of use claims 20-23.45-46 overlap with the claims of instant application. Therefore, if this application were granted patent, it would extend the monopoly of the above stated application(s).

5. Claims1, 19,20-23,24,25 and claims dependent on these claims are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1,19, 20-23,24,25,32,33, and claims dependent on these claims of copending Application No. 09695040, filed 10/24/2000. Although the conflicting claims are not identical, they are not patentably distinct from each other because the compounds of ref.'040 generic claim 1, composition clam 19, intermediates' claims 24,25, and method of use claims 20-23,32,33 overlap with the claims of instant application. Therefore, if this application were granted a patent, it would extend the monopoly of the above stated application(s).

6. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims1, 12,19,20-23,24,25, and claims dependent on these claims are rejected under 35 U.S.C. 102(b) as being anticipated by Franke et al (Helvetica Chemica Acta 58, 268-78(1975). Franke teaches compounds and derivatives with a core:"R-S-Phenyl-CH=CH-R' wherein R is substituted phenyl and R' is –COOH or its modifications as claimed herein". See e.g. Compounds # 47-49 in Table 1 of page 273. Instant claims overlap with the ref. compounds.

9. Claims1, 12,19,20-23,24,25, and claims dependent on these claims are rejected under 35 U.S.C. 102(b) as being anticipated by Ohno et al (GB 2117760 dated 10/19/1983). Ohno teaches compounds and derivatives with a core:"R1-pyridine-X-Phenyl-C (H)=CR2-CO-Y wherein X is –O- or –S-, R1 & R2 are each H or alkyl, Y is –OH, -OR5 or NR4R5 or its modifications as claimed herein". See e.g. Compound of Example 4 in page 4, compound of Example 2 in page 3, lines 51-63 respectively, compounds of claim 1,claims 7-8 (=pyridylthio-phenylpropenonate, claim 9(=thiopyrano-pyrimidine in page 8, and the compounds of the abstract. Instant claims overlap with the

ref. compounds. **Note, ref.'760 additionally teaches making of pharmaceutically acceptable salts and utility of compounds and their salt as inhibitors of Thromboxane A2, and their inhibitory activity on platelet aggregation induced by arachidonic acid and collagen (see Tables 1 and 2 in page 6, and abstract) as claimed herein.**

10. Claims1, 12,19,20-23,24,25, and claims dependent on these claims are rejected under 35 U.S.C. 102(b) as being anticipated by Bernardon et al (WO 9822423 dated 5/1998, also cited as Chemical Abstract DN 129:40990). The ref.'423 teaches compounds of Formula I with a core:" (Un) substituted phenyl-S- (UN) substituted divalent (benzene, furan, thiophene, pyridine)-CH==CH-R1 wherein R1 is Me, CH2OR5, OR5, COR6 (R5 = H, alkyl, acyl; R6 = H, alkyl, (UN) substituted NH2 or OH". See ref.'423 compounds 1(a) & 1(b) in Figure ½ & compounds of Formula (I)(= Substituted phenyl-X-Ar-Y-R1, wherein Ar is aryl or heterocycle, -Y-R1 =- CH=CH-COOH or its derivatives as claimed herein) in claim 1 in page 47. This core and compounds overlap with the instant claim(s).

11. Claims1, 12,19,20-23,24,25, and claims dependent on these claims are rejected under 35 U.S.C. 102(b) as being anticipated by Greenspan et al (WO 9813347 dated 4/1998, also cited as Chemical Abstract DN 128:257229). The ref.'347 teaches compounds of Formula I (see claim 1 in page 43) with a core:" [COOH/CH2OH (or Tetrazole/heterocycle-S)] -Phenyl or pyridine (-CR1=CH-CONR3R2) -S- (un) substituted Aryl or heterocycle" These compounds overlap with the instant claim(s). Note, the ref.'347 also teaches pharmaceutical compositions & the utility for treating inflammatory diseases as claimed herein.

12. Claims1, 12,19,20-23,24,25, and claims dependent on these claims are rejected under 35 U.S.C. 102(b) as being anticipated by Bernardon et al (EP 722928 dated 7/1996, also cited as Chemical Abstract DN 125:167598). The ref. '928 teaches compounds of Formula I with a core:" substituted phenyl-S- substituted Phenyl.-bridge(= -CR3=CR1R2 = -(un) modified cinnamide). See compounds of claim 1 in page 17, and compounds I(e), (I)f in Figure 2 of page 22 respectively. This core and compounds overlap with the instant claim(s).

13. Claims1,12,19,20-23,24,25, and claims dependent on these claims are rejected under 35 U.S.C. 102(b) as being anticipated by Miyamoto et al (EP 081321 dated 8/15/1983). The ref. '321 teaches compounds of Formula I with a core:" substituted phenyl-S- substituted Phenyl. See compounds XXIII; XVII; VIIIa; VIIIb in page 23 and definition of R4 on page11 lines 15-17". **This core and compounds overlap with the instant claim(s) related to compounds and intermediates as well**.

14. Claims1, 12,19,20-23,24,25, and claims dependent on these claims are rejected under 35 U.S.C. 102(b) as being anticipated by Andree et al (DE 4030041 dated 12/4/1992 also cited as Chemical Abstract DN 117:111634). The ref. '243 teaches compounds of Formula I in claim 1 on page 41 with a core:" substituted Heterocycle-Q1-(UN) substituted Phenyl with Z)-Q2- (UN) substituted heterocycle". See claim 1 wherein Z is a bridge –CR1 = CR4R3 (= -CH=CH-COOH/CONH2). This core and compounds overlap with the instant claim(s).

15. Claims1, 12,19,20-23,24,25, and claims dependent on these claims are rejected under 35 U.S.C. 102(b) as being anticipated by Drews et al (EP 459243 dated 3/1992 also cited as Chemical Abstract DN 116:151783). The ref. '041 teaches compounds of Formula I with a core:" substituted Heterocycle-Q- (UN) substituted Phenyl with (R3) m)-(C=Z)-R4 wherein the bridge –C (=Z) -CR4 (is= -CH=CH-COOH/CONH2). This core and compounds overlap with the instant claim(s).

Claim Rejections - 35 USC § 112

16. The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

17. Claims1, 12,13,19,20-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

18. Claim1 is rejected under 35 U.S.C. 112 Para second because they recite(where applicable for variables R1,R3,R10,R11, Ar,) " aryl, heterocyclyl, heterocyclylalky , heterocyclylsulfonylaminocarbonyl, heterocyclylcarbonyl, heterocyclylaminocarbonyl etc." for variables e.g. R10,R11, Ar. This is indefinite because the applicants do not exactly state which heteroatoms are present in these rings, how many of each heteroatoms(s)are present in these rings, where is exact point of connection with the core, and what SIZE RINGS ARE INTENDED AND HOW MANY RINGS ARE PRESENT.

19. Claim 12 as recited on page 287 last line misses the; at the end of the line. Correction is required.

20. Claim 12 as recited on page 292 line misses "sulfide; . Correction is required.

21. Claims 20-23,32,33 recite:" administration of a compound or composition". Correction to:" administration of a therapeutically effective amount of a compound or a therapeutically effective amount of a composition" is required.

22. Claims 20-23,32,33 recite:"administration", but do not exactly and definitely recite the mode of administration. Correction is required.

23. Claims 20-23,32,33 recite:" inflammation, immune response, cerebral vasospasm". Claims remain silent about what is exactly and definitely included or excluded from the stated disease or response.

24. Claim 1 recites constituents on to AR group in page 272-272 as:" m. amino carbonyl". This is not possible because the substituent –NH-CO- is not a bridge. Correction is required.

25. Claims 20-23,32,33 remain silent about the biological/pharmacological activity with which the diseases or responses are associated. This is not the exact and definite way of claims a method of treatment for a single disease.

26. Claims 12,13 are rejected as failing to comply with 37CFR1.141(a). The claims are more than a reasonable number of species. 37CFR1.141(a). Provides for a reasonable number of species to be examined with the genus. Claims 12,13 are an aggravated, multiple page **(pages 274-302 consisting of more than 500 compounds with different molecules)**, and examples of listing ultimate species in one claim.

Claims 12,13 are not Markush claims, see claim 1, and are listing of ultimate species to save the application fees.

Applicants are reminded that although the claims are interpreted in light of the specification, critical limitations from the specification cannot be read into the claims (see e.g. In re Van Guens, 988 F. 2d 1181, 26 PSPG 2d 1057 (Ded. Cir. 1991). Accordingly, without the recitation of all these critical limitations, the claims do not adequately define the instant invention.

Claim Rejections - 35 USC § 112

27. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

28. Claims20-23, 32,33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling **for a single specific and exact** disease related to inflammation, does not reasonably provide enablement for a generic inflammation, suppressing immune response, cerebral vasospasm. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. Specification in page 4 describes and includes diseases as:" notably acute and chronic inflammatory diseases, autoimmune diseases, tumor metastasis, allograft rejection, and reperfusion injury.

29. In cases directed to chemical compounds, which are being used for their physiological/biological activity, the scope of the claims must have a reasonable correlation to the scope of enablement provided by the specification. See in re Surrey 151 USPQ 724 regarding sufficiency of disclosure for a Markush group and In re Wiggins 179 USPQ 421.

30. "Compounds, pharmaceutically acceptable salts of prodrugs, and composition thereof" as recited in the claims read on all such moieties regardless of complexity of structure and point of attachment to the aliphatic or carboxylic or aromatic or heterocyclic core or bridge/chain for which there is no sufficient teaching how to make and how to use at any one selective location among the many possible sites present. The situation is more confusing when a skilled person in the art tries to visualize the multiple possibilities of combining a compound of claim 1(or claims dependent on it) and/ or its pharmaceutical composition for treating a patient having diseases or conditions associated with inflammation, suppressing immune response, cerebral vasospasm in general. Applicants provide no reasonable assurance that any and all derivatives of the instant compounds and their compositions as outlined, will have ability to generate the compounds in vivo or in vitro by one or more processes.

31. In evaluating the enablement question, several factors are to be considered. In re Wands, 8 USPQ 2d 1400 (Fed. Cir. 1988); Ex parte Forman, 230 USPQ 546. The factors include:***(1).*** The nature of invention;***(2).*** the state of prior art ;***(3).*** the predictability or lack thereof in the art;***(4).*** the amount of direction or guidance present;***(5).*** the

presence or absence of working examples;*(6).* the breadth of the claims, and *(7).* the quantity of experimentation needed.

1). The nature of the invention: The compounds and their method of use claim(s) are drawn in part to use them for treating a patient having diseases or conditions associated with inflammation, suppressing immune response, cerebral vasospasm and diseases yet to be discovered.

2). The state of prior art: There are no known compounds of similar structure (i.e. compounds of the invention which have been demonstrated for the treatment of infection or disease as recited here in a generic way.

3). The predictability or lack thereof in the art: It is presumed in the use for patient(s) who are humans or animals suffering from disease(s) related to a generic activity as claimed herein, there is a way of identifying those patient(s) who may develop any kind of physiological conditions including (but not limited to) a single disease. There is no evidence of record, which would enable the skilled artisan in the identification of the patient(s) who have the potential of becoming afflicted with the physiological conditions related to inflammation, suppressing immune response, cerebral vasospasm and diseases yet to be discovered and as claimed herein.

4). The amount of direction or guidance present and 5).: The presence or absence of working examples: There are no doses present to direct one to treat a potential host from an infection or disease, and other multiples of physiologically related condition(s) of various types. Specification remains silent about the exact patient-dosage regime, and claims also remain silent about the exact method or step of administration for treating such diseases.

6). The breadth of the claims: The claims are drawn to physiological conditions (not limited to) and not for treatment of a single, specific and exact inflammation, suppressing immune response, cerebral vasospasm and diseases yet to be discovered, which are not related and whose treatment(s) is unknown by a single compound of instant invention.

7). The quantity of experimentation need would be and undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan for the many reasons stated above.

Discussion about inflammatory diseases and conditions:

Enablement for the scope of "inflammatory diseases" generally is not present. For a compound or genus to be effective against inflammation generally is contrary to medical science. Inflammation is a process, which can take place in virtually any part of the body. There is a vast range of forms that it can take, causes for the problem, and

biochemical pathways that mediate the inflammatory reaction. There is no common mechanism by which all, or even most, inflammations arise. Mediators include bradykinin, serotonin, C3a, C5a, histamine, assorted leukotrienes and cytokines, and many, many others. Accordingly, treatments for inflammation are normally tailored to the particular type of inflammation present, as there is no, and there can be no "magic bullet" against inflammation generally.

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Inflammation is the reaction of vascularized tissue to local injury; it is the name given to the stereotyped ways tissues respond to noxious stimuli. These occur in two fundamentally different types. Acute inflammation is the response to recent or continuing injury. The principal features are dilation and leaking of vessels, and recruitment of circulating neutrophils. Chronic inflammation or "late-phase inflammation" is a response to prolonged problems, orchestrated by T-helper lymphocytes. It may feature recruitment and activation of T- and B-lymphocytes, macrophages, eosinophils, and/or fibroblasts. The hallmark of chronic inflammation is infiltration of tissue with mononuclear inflammatory cells. Granulomas are seen in certain chronic inflammation situations. They are clusters of macrophages, which have stuck tightly together, typically to wall something off. Granulomas can form with foreign bodies such as aspirated food, toxocara, silicone injections, and splinters.

Otitis media is an inflammation of the lining of the middle ear and is commonly caused by Streptococcus pneumoniae and Haemophilus influenzae. Cystitis is an inflammation of bladder, usually caused by bacteria. Blepharitis is a chronic inflammation of the eyelids that is caused by a staphylococcus. Dacryocystitis is inflammation of the tear sac, and usually occurs after a long-term obstruction of the nasolacrimal duct and is caused by staphylococci or streptococci. Preseptal cellulites is inflammation of the tissues around eye, and Orbital cellulites is an inflammatory process involving the layer of tissue that separates the eye itself from the eyelid. These life-threatening infections usually arise from staphylococcus. Hence, these types of inflammations are treated with antibiotics.

Discussion about non-steroidal anti-inflammatory agents:

32. Certain types of anti-inflammatory agents, such as non-steroidal anti-inflammatory medications(Ibuprofen and naproxen) along with muscle relaxants can be used in the non-bacterial cases. The above list is by no means complete, but demonstrates the extraordinary breadth of the causes, mechanisms and treatment (or lack thereof) for inflammation. It establishes that it is not reasonable to any agent to be able to treat inflammation generally.

33. Following are a few of the many references cited to show the state of art(s):

34. Cell adhesion & cinnamides: Debnath et al(PubMed Abstract 12659746, also cited as Bioorg Med. Chem. 11/8,1615-9(2003)) state that:" Steric effect on the arylthio ring and lipophilic substitutions as 2,3-positions, especially 2,3-disubstitution with cl or CF3 or both on cinnamides were conductive to activity, whereas simultaneous presence of methoxy group at arylthio ring and –NCOCH3 group at heterocycle ring of cinnamides were detrimental to activity in antagonism of biochemical ICAM-1/LFA-1 interaction". Therefore, a single compound of this application can not cure all diseases of claims 20-23,32,33.

35. **Inflammation & inhibition and cell adhesion:** Stopfer et al(PubMed Abstract 15030519, also cited as Clin. Exp. Immunol.,136/1,21-9(2004) state that:" A combination tratment with reagents blocking T cell-mediated perpetuation of chronic inflammation such as LtbetaR-Ig together with firect anti-inflammatory reagents such as TNF inhibitors could constitute a promising treatment strate for chronic colitis".

36. Inflammation and cinnamides: Greenspan et al(PubMed Abstract 9888841, also cited as J. Med. Chem.,42/1,164-72(1999)) state that:" Several compounds of carboxy-substituted cinnamides series were found to significantly inhibit edema formation and mueloperoxid activity in this model up to 17 hr after oral adminitration in vitro". No such data exists for instant compounds in the specification.

37. **Arylsulfides and inhibition:** Brannigan et al(PubMed Abstract 950649, also cited as J. Med. Chem. 19/6,798-802(1976). Stat that:" Fout of the compounds had activity roughly comparable to aspirin. Phenylbutazone in one or the other of these assays. Sulfoxides did seem especially promising as a class and usually were less active than the corresponding sulfides. The two most interesting compounds in these assays, phenylthio-phenyl acetic acid and its oxide had no significant activity in adjuvant arthritis".

38. Mode of administration and effect produced by other products: Yamada et al(PubMed Abstract 14744884, also cited as Invest.Ophthalmol. Vis. Sci. 45/2,448-54(2004)) state that:" The intravenous transfer of peritoneal Mps from(NACOMe)(2)-treated mice prolonged corneal allograft survival". Therefore, mode or step of administration affects the treatment. Applicants do not recite the specific mode of administration of a compound or its pharmaceutical composition for diseases recited.

39. Cerebral vasospasms and treatments: Misra et al(PubMed Abstract 14977060, also cited as Neurol. Res. 26/1,67-73(2004)) state that:" Cerebral ischemia to posterior fossa is more critical and difficult to treat. This is primarily due to complex anatomy and physiology of posterior fossa cerebal circulation....Improving the blood flow in the areas of brain at risk in properly selected patients could prevent impending cerebral ischemia and infrarction".

40. Existing compounds for treating cerebral vasospasm: Lesley et al (PubMed Abstract 12812961, also cited as AJNR Am. J. Neuroradiol. 24/6,1234-6(2003)) state that:" We conclude that use of transdermal Nitroglycerine oilment/paste is a simple noninvasive technique to reduce intracranial vasospasm".

41. Specification on pages 262-269 recites various test(s) and assay method for binding activity of ICAM-1/LFA-1 receptor(s). Results as recited in lines 4-7 of page 263 state that:" Biologically relevant activity of the compounds in this invention is confirmed using a cell-based adhesion assay, which measures their ability to block the adherence of JY-8 cells to immobilized ICAM-1...., and on page 264, it is concluded that the compounds of the present invention exhibited blocking activity in the above assay. Inhibition at 4uM was demonstrated".

42. The ICAM-3/JY-8 cell adhesion assay has been concluded on page 265, lines 4-5 as:" Compounds of the present invention exhibited blocking activity in the above assay. 100% INHIBITION AT 0.6 uM WAS DEMONSTRATED. Thus, applicants have not presented the exact data for the compounds of instant invention. Various other methods/assay protocols are recited in pages 265-269 and recited as:" the ability to treat various diseases and conditions can be demonstrated by these methods". Specification remains silent about the exact data obtained for the exact compounds made and put through these tests. Therefore comparison(s) cannot be made to check what actually was obtained at various levels of concentration(s) other than 4 or 0.6 uM.

These results will only serve for the preliminary screening of many compounds, and not for treating the diseases as claimed herein.

The facts as provided above do support the need for additional quantity of experimentation which would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the method of treatment for various disorders/conditions related to inflammation, cancer, and other diseases.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of instant compounds to treat various disorders/diseases related to receptors as recited in specification only.

When the best efforts have failed to achieve a goal, it is reasonable for the PTO to require evidence that such a goal has been accomplished, *In re Ferens*, 163 USPQ 609. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs. Novo Nordisk*, 42 USPQ2nd 1001, 1006.

Conclusion

Allowable Subject Matter

43. Claims11, 19 related to compounds of claim 11, and a composition of the same if limited to the search done, would be considered for allowance if rewritten to overcome the rejection(s) under 35 U.S.C. 112, second paragraph and others, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

44. A method of use claim would also be considered for allowance, if limited to a specific, single, and exact disease, provided additional supporting data is made available in reply to this action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sudhaker B. Patel, D.Sc.Tech. whose telephone number is (571) 272-0671.

The examiner can normally be reached on 6:30 to 5:00 pm (Monday-Thursday). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Mukund J. Shah can be reached on (571) 272 0674 or Sr. Examiner Mr. Richard Raymond at (571) 272 0673 or Mr. James O. Wilson at (571) 272-0661.

The fax phone numbers for the organization where this application or proceeding is assigned are 703 308 4556 for regular communications and 703 308 4556 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 308 1235.Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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